# PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017 |
| **AUTHORS** | Kurani, Shaheen; McCoy, Rozalina; Inselman, Jonathan; Jeffery, Molly; Chawla, Sagar; Finney Rutten, Lila; Giblon, Rachel; Shah, Nilay |

## VERSION 1 – REVIEW

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| **REVIEWER** | Bradley D Stein<br>RAND Corporation<br>United States |
| **REVIEW RETURNED** | 18-Nov-2019 |

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| **GENERAL COMMENTS** | In this manuscript, the authors examine the relationship between county-level area deprivation and patterns of both opioid prescribing and drug-poisoning mortality. A number of studies have examined the relationship between various dimensions of the opioid crisis, and a variety of socio-economic factors that are positively associated with opioid crisis related harms, with Chris Ruhm's work and Case and Deaton's "Deaths of Despair" research being among the most widely known and cited. In this study, the authors also examine this issue, using 2012-2017 IQVIA data and CDC NVSS data, as well as ACS data to create an area deprivation index. The relationship between socioeconomic disadvantage and the opioid crisis is an important one, and the use of the ADI is novel. However, there are a number of issues that diminish my enthusiasm for the current manuscript.<br><br>1) Given how much work has already been done examining the relationship between socioeconomic factors and dimensions of the opioid crisis, a more thorough review of the literature, and greater efforts to highlight the contribution of this analysis, would have strengthened the manuscript. As written, while the use of the ADI is novel, the general story is one that has been examined in quite a few other papers.<br>2) The authors mention heroin and fentanyl a few times, but never discuss that since 2011 opioid analgesic prescriptions have been decreasing, with overdose deaths driven first by heroin, and in the last several years by fentanyl, with some studies suggesting that efforts to decrease opioid analgesic misuse substantially contributed to the increase in overdose deaths by increasing use of heroin. This information seems critically important to the issue being examined.<br>3) A relatively minor issue, but the authors included buprenorphine in the list of opioids identified, but most buprenorphine is used for treatment of OUD, and is not commonly included in lists of opioid analgesics used for pain management. |

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| | 4) For the county level drug poisoning mortality, there isn't enough information in the methods for me to tell if they used all OD deaths or opioid related OD deaths. County level OD deaths shouldn't be used because of data issues (see a recent paper by Chris Jones and colleagues)<br>5) There are quite a few places where the authors make assertions that would benefit from a cite supporting the assertion. This is particularly true in places in which the assertion does not seem consistent with current beliefs. For example, at the beginning of the second paragraph of the conclusion, the authors state that improved OUD treatment and greater availability of naloxone likely contributed to the decrease in rates of opioid prescribing. While I'm aware of multiple studies examining a variety of factors contributing to decreases in opioid prescribing, such as PDMPs, lock-in programs, CDC guidelines, and high dose prescription limits, I'm unaware of studies showing any causal relationship with naloxone or OUD treatment.<br>6) The authors discuss using ADI to better target programs related to the opioid crisis. I'm not sure I understand why they think this would be better than actually just using information about overdose deaths and opioid analgesic prescribing to target those communities. Even if there is a relationship with ADI, it is both possible and more precise to directly measure those things you care about and what to target. Further justification of why to use the ADI instead would strengthen the manuscript.<br>7) In Table S2, it appears that the rate of opioid prescribing in their analysis is lower among individuals >65 years than among individuals in younger cohorts. This finding is quite unexpected, as almost all if not all other studies I'm familiar with find that the elderly, who are more likely to suffer from a range of painful conditions, are much more likely to receive opioids than younger individuals. I'm wondering if this is maybe a typo? If not, this is the type of result that suggests there might have been an issue with the underlying data or analysis, and I'd encourage the authors to re-examine their results.<br>8) The authors are careful to use association and not causality in the abstract, consistent with their analytic approach, but there are a number of places throughout the manuscript in which they imply causality. This language should be modified. |

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| **REVIEWER** | Rebecca Haffajee, JD, PhD, MPH<br>RAND Corporation, U.S.A. |
| **REVIEW RETURNED** | 27-Nov-2019 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review "Place, Poverty, and Prescriptions: Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality form 2012-2017." Overall, this paper presents some interesting insights into the opioid crisis and social determinant correlates with opioid harms. Particularly novel is the derivation of the time-varying area deprivation index (ADI) for each county using 17 county-level factors (selected using factor analysis and weighted). Comparing opioid prescriptions and drug overdose mortality to ADI quintiles presents provides new insights into the positive relationship between area deprivation and opioid harms.<br><br>I have a few broad comments to improve the paper, followed by some specific recommendations:<br><br>Broad Comments:<br>-Although this presents a novel approach to thinking about the opioid crisis, I found the discussion and policy implications to be somewhat |

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| | lacking. General statements that area deprivation must be incorporated into our opioid crisis response do not advance the narrative beyond what we already knew. I would have liked to have seen more specific recommendations, perhaps tied to the 17 factors used to derive the ADI, of what policies the authors recommend be further studied or pursued. 60% of higher deprivation counties is a lot of counties -- so the vague policy recommendations for this majority of counties is not all that helpful for policymakers.<br>-Additional discussion of the study limitations is required. For instance, drug overdose deaths captures more than opioid-related deaths (and although drug use seems to be somewhat related across classes of drugs, we don't yet understand this relationship well). I would recommend doing a sensitivity analysis using just opioid related deaths (although I know there will be less counties to include and some measurement concerns at the county level) to see if the results are consistent with the all drug overdose mortality results.<br>-I would appreciate further discussion about why the opioid prescriptions and ADI have a linear relationship (figure 4), whereas the drug mortality seems to peak in ADI Q4 (figure 5)? Why would Q5 have modestly lower mortality in every year?<br><br>Specific Comments:<br>-Should buprenorphine (and perhaps methadone) be included in the opioid prescription counts? These treatments are typically excluded when considering harms. (or at least conduct a sensitivity analysis)<br>-I recommend considering adjusting the maps (figures 1-3) to include the same thresholds across years (rather than quintiles separately calculated each year). This way we could see the changes in harms across counties over time.<br>-Update statistics in first few sentences, p. 4, to 2017 data, rather than 2016.<br>-Add word "prescription" before opioids, line 19, p. 5.<br>-Lines 24-26, p.2: yes, outcomes should be tracked in parallel, but need to include appropriate controls for illicit drug supply (which are often omitted) to avoid incorrect imputation of mortality harms attributable to opioid prescribing reductions.<br>-Could you provide more detail about the accuracy of imputation methods and any potential bias, lines 8-10, p. 9?<br>-To your comment about disparities in opioid Rx rates being attributable to greater availability of opioid prescribers in highly deprived counties, could you please add some measures of workforce to the regressions? I actually suspect the reverse is true -- that PCP and pain specialists may be more densely distributed in lower deprivation communities. |

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| **REVIEWER** | Jennifer Bobb<br>Kaiser Permanente Washington Health Research Institute |
| **REVIEW RETURNED** | 24-Dec-2019 |

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| **GENERAL COMMENTS** | In this paper the authors examine the association between county-level deprivation as quantified by a summary index measure (ADI score) and two outcome measures: county-level opioid prescription fills and county level drug-poisoning mortality rates. For the methods, they applied a two stage modeling approach, where at the first stage, a spatial-temporal model was fit to estimate the county-specific rates of deaths per 100,000 residents, and at the second stage a negative binomial regression model was applied to estimate the association between ADI quintile and each of the outcomes. I have a few major comments on the statistical methods and |

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| | presentation of the results, as well as several minor comments to improve the paper.<br><br>Major comments<br><br>- Tje authors mention that "hierarchical Bayesian methods with spatial and temporal random effects generated adjusted county-level drug-poisoning mortality rates per 100,000 residents" (p. 8). More detail is needed beyond just providing a citation. Perhaps a statistical appendix can describe precisely what the modeling approach was, if there is insufficient room in the main manuscript text. In addition, it wasn't clear to me whether this model fit to all of the outcomes, or just to the drug-poisoning outcome. In addition, there is no rationale for using a two-stage modeling approach to first estimate county-level rates and the apply a second-stage model to estimate the association of interest. This needs to be justified and explained.<br><br>- Standard errors from the outcome regression model account for repeated measures from same county over time, but do not account for correlation of rates across neighboring counties (e.g., via a CAR model), or for uncertainty in the estimated rates resulting from fitting the spatial-temporal model. A unified modeling approach that includes the covariates and ADI measure simultaneously within the spatial-temporal model would address all of these sources of correlation and uncertainty.<br><br>- Did the negative binomial models account for the different population size in each county? Bigger counties will have more precise estimates of rates than smaller counties, and this needs to be accounted for (e.g., via an offset term). In this case it seems as if the authors used a first-stage model to estimate the rates per 100,000 individuals. Presumably the model outputs some time of uncertainty measure for the county-specific rates and this would need to be incorporated into the second stage model that estimates the association between ADI quintile and the outcome rates.<br><br>- "Rates of opioid prescriptions decreased consistently between 2012 and 2017 within each ADI quintile (Figure 4)." (p. 10). This is a little misleading as a result. The model included main effects for calendar year and for ADI quintile; it therefore did not allow the relationship over time to vary across ADI quintile. In order to do that the model would need to include interaction terms in the model between year and ADI quintile. The authors should clarify whether they intended to explore interaction, and if so how the interaction was modeled. Otherwise, the text should be revised to avoid any misleading interpretations of the modelng results.<br><br>Minor comments<br><br>- Figures 1-3: It is hard to see individual county esimates when all 6 maps are shown. One approach would be to plot the mean rates across the 6 years since it looks like most of the variability is spatial as opposed to temporal.<br><br>- Abstract: should say in the Methods that the exposure was quintiles of ADI -- this is not mentioned until the Abstract conclusion |

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| | - Strengths and Limitations: "This study is limited by potential imputation" -- more detail is needed by what is meant here. Do you mean that there could be bias due to non-trivial missing data?<br><br>- "All U.S. counties with opioid prescription and drug-poisoning mortality data available each year between 2012 and 2017 were included in the study sample. Counties without data for all six years of the study were excluded from the sample" (p. 7). Given that the analysis models annual county-level rates, couldn't counties that had at least one year of data be included?<br><br>- "County demographic information necessary for ADI derivation was ascertained from 2012-2016 and 2013-2017 5-year ACS estimates...calculated separately each year" (p. 7).<br>I found this language confusing -- how are the 5-year estimates calculated separately by year?<br><br>- "We calculated modified ADI scores, using the Singh method,15 for all 3,142 counties in the U.S. using 5-year ACS estimates (Figure 3)." Is there a single ADI score per county, or could the scores vary over time?<br><br>- One suggestion to improve the paper flow would be to move the description of the exposure to its own section above the "Statistical Analysis" section. Then the Statistical Analysis section can focus on how you estimated the effect of the exposure (ADI quintile) on each of the outcomes<br><br>- "Predicted margins for adjusted prescription rates and drug-poisoning mortality were assessed by ADI quintile across all years." More details are needed on exactly what was done here, or at least a citation should be provided.<br><br>- "county-level estimates for age" were adjusted for in the model. There are many options for this (e.g., mean or median age, % within different categoreis). What exactly was done?<br><br>- How did the authors handle the ICD-9 to ICD-10 transition that occurred during the study period?<br><br>- In the results section is is difficult to tell whether estimates being presented are from fitting a model, or whether estimates are raw rates, when describing the trends in prescriptions (e.g., paragraphs 1-2 of Results).<br><br>- Figure 2: Are these the raw rates or the smoothed rates from fitting the spatial-temporal model. These rates look a lot smoother than I would expect if they are the raw rates.<br><br>- Point estimates for Q5 are lower than for Q4 of the ADI in Figure S1, but in Table 1 Q5 has a higher IRR than Q4. Could you explain this seeming discrepancy?<br><br>- Models assume that the IRR of ADI quintile with the outcomes is constant by year; did you test this assumption?<br><br>- "Each successively less deprived ADI quintile displayed a |

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| | smaller decrease in prescription rate." (p. 10). Is this referring to descrease over time? Again, this sounds like you are commenting on interaction between ADI and calendar time (see related comment above), which was not explicitly modeled.<br><br>- "Although the absolute opioid prescription rate decrement was largest in ADI Q5, the proportion of the decrease was similar across all ADI quintiles." I found this sentence confusing. Perhaps the authors could point to the specific estimates and/or Figure that this is referencing. What do you mean by "decrement" -- does this mean change over time, or are you refering to an IRR < 1?<br><br>- Did the authors consider the potential for confounding by region. Some regions may have greater deprivation and also greater rates of opioid prescriptions and/or drug poisoning mortality, regardless of their deprivation. May want to present results stratified by region in a supplement./p><br><br>- "There were no major geospatial changes in the patterns of deprivation, opioid prescriptions, or drug-poisoning mortality during the study period" (p. 12). This is a strong assertion. How was this tested in the data?<br><br>- I'd suggest to include in the footnote to Figure 4 a 1-sentence description of the model including the covariates. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Bradley D Stein
Institution and Country:
RAND Corporation
United States
Please state any competing interests or state 'None declared': None declared

1) Given how much work has already been done examining the relationship between socioeconomic factors and dimensions of the opioid crisis, a more thorough review of the literature, and greater efforts to highlight the contribution of this analysis, would have strengthened the manuscript. As written, while the use of the ADI is novel, the general story is one that has been examined in quite a few other papers.

**Thank you for this constructive feedback. To our knowledge, this is the first study to examine the opioid crisis using a composite measure of socioeconomic factors rather than singular constructs such as race, sex, or income. While prior studies have described the rates of opioid prescriptions and drug poisoning mortality, we were able to quantify the impact of area-level social determinants of health on both outcomes that was independent of previously examined constructs. This has important implications for public health, policy, and resource allocation. We explicitly clarify this in the revised manuscript. We highlight in the background section that the recent focus on decreasing the supply/availability of prescription opioids may have led to a divergence between opioid prescribing and drug-poisoning mortality in areas where opioid use may be low but drug mortality remains high. Unlike other papers, our work is able to parse this out by examining these two outcomes in parallel. Thus, our work demonstrates that it is possible and advantageous to use ADI to understand the geographic localization of the opioid crisis and gain insight into the communities that could benefit from the targeted interventions.**

2) The authors mention heroin and fentanyl a few times, but never discuss that since 2011 opioid analgesic prescriptions have been decreasing, with overdose deaths driven first by heroin, and in the

last several years by fentanyl, with some studies suggesting that efforts to decrease opioid analgesic misuse substantially contributed to the increase in overdose deaths by increasing use of heroin. This information seems critically important to the issue being examined.
**We absolutely agree with the reviewer and this is a key point in our discussion and findings (pages 5, 13).**
3) A relatively minor issue, but the authors included buprenorphine in the list of opioids identified, but most buprenorphine is used for treatment of OUD, and is not commonly included in lists of opioid analgesics used for pain management.
**We agree that buprenorphine is not comparable to other opioids and is not used for pain management; however, the data used for this study was downloaded from the CDC and could not remove buprenorphine from among the included drugs.**
4) For the county level drug poisoning mortality, there isn't enough information in the methods for me to tell if they used all OD deaths or opioid related OD deaths. County level OD deaths shouldn't be used because of data issues (see a recent paper by Chris Jones and colleagues)
**We appreciate this feedback and have clarified in the manuscript (page 8) that we specifically examined all drug-poisoning deaths and not just opioid-related OD deaths.**
5) There are quite a few places where the authors make assertions that would benefit from a cite supporting the assertion. This is particularly true in places in which the assertion does not seem consistent with current beliefs. For example, at the beginning of the second paragraph of the conclusion, the authors state that improved OUD treatment and greater availability of naloxonelikely contributed to the decrease in rates of opioid prescribing. While I'm aware of multiple studies examining a variety of factors contributing to decreases in opioid prescribing, such as PDMPs, lock-in programs, CDC guidelines, and high dose prescription limits, I'm unaware of studies showing any causal relationship with naloxone or OUD treatment.
**Thank you for bringing this to our attention. We have changed the phrasing of the sentences in the second paragraph of the conclusion and ensured that all citations are included as appropriate.**
6) The authors discuss using ADI to better target programs related to the opioid crisis. I'm not sure I understand why they think this would be better than actually just using information about overdose deaths and opioid analgesic prescribing to target those communities. Even if there is a relationship with ADI, it is both possible and more precise to directly measure those things you care about and what to target. Further justification of why to use the ADI instead would strengthen the manuscript.
**We believe that ADI can be used as a risk stratification tool for adverse health behaviors and outcomes and allow us to target interventions proactively to at risk communities before adverse outcomes occur.**
7) In Table S2, it appears that the rate of opioid prescribing in their analysis is lower among individuals >65 years than among individuals in younger cohorts. This finding is quite unexpected, as almost all if not all other studies I'm familiar with find that the elderly, who are more likely to suffer from a range of painful conditions, are much more likely to receive opioids than younger individuals. I'm wondering if this is maybe a typo? If not, this is the type of result that suggests there might have been an issue with the underlying data or analysis, and I'd encourage the authors to re-examine their results.
**Thank you for calling out this point that could be confusing to many readers. This was not a typo. The age variable does not refer to the age of the individual taking the opioid medication or dying from drug poisoning, but instead to the distribution of ages of people living within each specific county. Thus, our models adjust for the percentage of a county with individuals 18-44, 45-64, and 65+ and find that for every 1 percentage point increase in residents above 65 years of age, there is a 1% increased risk in opioid prescription fills for that county. We clarify this in our revised manuscript so as to avoid this confusion.**
8) The authors are careful to use association and not causality in the abstract, consistent with their analytic approach, but there are a number of places throughout the manuscript in which they imply causality. This language should be modified.
**We have modified the language throughout the manuscript.**

Reviewer: 2
Reviewer Name: Rebecca Haffajee, JD, PhD, MPH
Institution and Country: RAND Corporation, U.S.A.
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the opportunity to review "Place, Poverty, and Prescriptions: Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality form 2012-2017." Overall, this paper presents some interesting insights into the opioid crisis and social determinant correlates with opioid harms. Particularly novel is the derivation of the time-varyig area deprivation index (ADI) for each county using 17 county-level factors (selected using factor analysis and weighted). Comparing opioid prescriptions and drug overdose mortality to ADI quintiles presents provides new insights into the positive relationship between area deprivation and opioid harms.

I have a few broad comments to improve the paper, followed by some specific recommendations:

Broad Comments:
-Although this presents a novel approach to thinking about the opioid crisis, I found the discussion and policy implications to be somewhat lacking. General statements that area deprivation must be incorporated into our opioid crisis response do not advance the narrative beyond what we already knew. I would have liked to have seen more specific recommendations, perhaps tied to the 17 factors used to derive the ADI, of what policies the authors recommend be further studied or pursued. 60% of higher deprivation counties is a lot of counties -- so the vague policy recommendations for this majority of counties is not all that helpful for policymakers.
**ADI is a risk stratification tool and we agree that it is important to understand which ADI components may be most influential in leading to this outcome, but that is outside of the scope of this study. We are pursuing that as our next step building upon this work. We believe our findings add to an existing body of literature that supports the need to consider social determinants of health to develop and target more tailored interventions to all counties.**
-Additional discussion of the study limitations is required. For instance, drug overdose deaths captures more than opioid-related deaths (and although drug use seems to be somewhat related across classes of drugs, we don't yet understand this relationship well). I would recommend doing a sensitivity analysis using just opioid related deaths (although I know there will beless counties to include and some measurement concerns at the county level) to see if the results are consistent with the all drug overdose mortality results.
**We agree that this would be ideal. However, the publicly available data from the CDC do not allow us to separate out just opioid-related deaths.**
-I would appreciate further discussion about why the opioid prescriptions and ADI have a linear relationship (figure 4), whereas the drug mortality seems to peak in ADI Q4 (figure 5)? Why would Q5 have modestly lower mortality in every year?
**Thank you for bringing this to our attention. The figure presented was predicting values based on an average ADI across all years which we now appreciate to be confusing given the presentation of the other data. We have fixed this and revised the figure accordingly.**
Specific Comments:
-Should buprenorphine (and perhaps methadone) be included in the opioid prescription counts? These treatments are typically excluded when considering harms. (or at least conduct a sensitivity analysis)
**Thank you for this suggestion. The CDC data we used are not available broken out by medication.**
I recommend considering adjusting the maps (figures 1-3) to include the same thresholds across years (rather than quintiles separately calculated each year). This way we could see the changes in harms across counties over time.
**We appreciate the insightful comment. As it stands, there is no acceptable threshold for where to cut off ADI. We therefore used quintiles, consistent with prior publications. Absolute deprivation and thresholds need to be informed by empirical evidence which is currently lacking but would be important to investigate in the future.**
-Update statistics in first few sentences, p. 4, to 2017 data, rather than 2016.
**Thank you for pointing this out. We have updated the statistics to reflect 2017 data.**
-Add word "prescription" before opioids, line 19, p. 5.
**This has been incorporated.**
-Lines 24-26, p.2: yes, outcomes should be tracked in parallel, but need to include appropriate controls for illicit drug supply (which are often omitted) to avoid incorrect imputation of mortality harms attributable to opioid prescribing reductions.
**Thank you for the comment. We do not have the data for illicit drugs, but one of the conclusions of the study is that the illicit drug supply must be contributing to the increase in mortality that is seen in our study.**

-Could you provide more detail about the accuracy of imputation methods and any potential bias, lines 8-10, p. 9?
**Potential sources of bias/inaccuracy for imputation method are: 1) it requires the assumptions that date are missing at random (MAR), 2) it generally underestimates the variance of the imputed data, and 3) it inflates the correlation between coefficients. However, studies have shown that in cases where missing data are MAR and comprise 10% or less of the total sample, the benefits of imputation outweigh the bias produced by discarding missing data. This study had less than 1% missing data for each year and fewer than 16 variables were imputed each year. As a result, the potential for bias is very low (total of 78 missing variable observations out of 320,484). https://mro.massey.ac.nz/bitstream/handle/10179/4355/Dealing_with_Missing_Data.pdf**

**We added the following detail to the manuscript:**
**"However, our study had less than 1% of missing data for each year and fewer than 80 variable observations were imputed in total. Thus, the potential for imputation bias is very low."**

-To your comment about disparities in opioid Rx rates being attributable to greater availability of opioid prescribers in highly deprived counties, could you please add some measures of workforce to the regressions? I actually suspect the reverse is true -- that PCP and pain specialists may be more densely distributed in lower deprivation communities.
**This is an interesting idea and would answer an important question and gap in the literature. It is outside the scope of this study, so we removed this section of the text from the revised manuscript.**

Reviewer: 3
Reviewer Name: Jennifer Bobb
Institution and Country: Kaiser Permanente Washington Health Research Institute
Please state any competing interests or state 'None declared': None declared

"Place, Poverty, and Prescriptions: Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality from 2012-2017"
In this paper the authors examine the association between county-level deprivation as quantified by a summary index measure (ADI score) and two outcome measures: county-level opioid prescription fills and county level drug-poisoning mortality rates. For the methods, they applied a two stage modeling approach, where at the first stage, a spatial-temporal model was fit to estimate the county-specific rates of deaths per 100,000 residents, and at the second stage a negative binomial regression model was applied to estimate the association between ADI quintile and each of the outcomes. I have a few major comments on the statistical methods and presentation of the results, as well as several minor comments to improve the paper.
Major comments
- Tje authors mention that "hierarchical Bayesian methods with spatial and temporal random effects generated adjusted county-level drug-poisoning mortality rates per 100,000 residents" (p. 8). More detail is needed beyond just providing a citation. Perhaps a statistical appendix can describe precisely what the modeling approach was, if there is insufficient room in the main manuscript text. In addition, it wasn't clear to me whether this model fit to all of the outcomes, or just to the drug-poisoning outcome. In addition, there is no rationale for using a two-stage modeling approach to first estimate county-level rates and the apply a second-stage model to estimate the association of interest. This needs to be justified and explained.
**Thank you for the opportunity to clarify. We did not perform the hierarchical Bayesian methods to produce the county-level estimates. These are methods performed by the CDC prior to publishing the rates online. We have clarified this in the manuscript.**
- Standard errors from the outcome regression model account for repeated measures from same county over time, but do not account for correlation of rates across neighboring counties (e.g., via a CAR model), or for uncertainty in the estimated rates resulting from fitting the spatial temporal model. A unified modeling approach that includes the covariates and ADI measure simultaneously within the spatial-temporal model would address all of these sources of correlation and uncertainty.

**Unfortunately, we do not have statistical software available to us that could account for spatial-temporal correlation and for the different population sizes in the counties (i.e., through a negative binomial regression with an offset term for county population).**

**To give a rough sense of how much of a problem this is, we compared coefficients and standard errors estimated by 3 models: 1. A linear regression using the rate per 100,000 residents as the dependent variable (i.e., not accounting for population size) with one year of data, 2. Same as one, but accounting for spatial correlation, and 3. A negative binomial model for a single year accounting for population size. All three approaches gave the same inference as the model in the manuscript.**

**In comparing models 1 and 2 (linear regression with and without correction for spatial correlation), the coefficients changed by less than 10%, and no inference changed. In comparing 1 and 3 (with and without correction for county population size), we calculated predictive margins after each regression for the quintiles of ADI and found that the predictions and their standard errors varied by about 1 to 2%.**

**Given these results, we believe that the findings are robust and that inference is unlikely to change with improved modeling specifications.**

- Did the negative binomial models account for the different population size in each county? Bigger counties will have more precise estimates of rates than smaller counties, and this needs to be accounted for (e.g., via an offset term). In this case it seems as if the authors used a first-stage model to estimate the rates per 100,000 individuals. Presumably the model outputs some time of uncertainty measure for the county-specific rates and this would need to be incorporated into the second stage model that estimates the association between ADI quintile and the outcome rates.

**Yes, our negative binomial regression was done in a single stage with an offset of county population.**

- "Rates of opioid prescriptions decreased consistently between 2012 and 2017 within each ADI quintile (Figure 4)." (p. 10). This is a little misleading as a result. The model included main effects for calendar year and for ADI quintile; it therefore did not allow the relationship over time to vary across ADI quintile. In order to do that the model would need to include interaction terms in the model between year and ADI quintile. The authors should clarify whether they intended to explore interaction, and if so how the interaction was modeled. Otherwise, the text should be revised to avoid any misleading interpretations of the modeling results.

**Thank you for your comment. We ran a sensitivity analysis to assess the impact of the interaction term which did not change the inference. We have updated the text to avoid any misleading interpretations of the model results.**

Minor comments

- Figures 1-3: It is hard to see individual county estimates when all 6 maps are shown. One approach would be to plot the mean rates across the 6 years since it looks like most of the variability is spatial as opposed to temporal.

**We are happy to include this information in a supplemental table if the reviewers and editors find this helpful.**

**Mean mortality rates (crude) per 100,000 people for each year were as follows:**
**2012: 14.0**
**2013: 14.6**
**2014: 15.5**
**2015: 17.0**
**2016: 19.6**
**2017: 21.1**
**Mean prescribing rates (crude) per 100 people for each year were as follows:**
**2012: 96.7**
**2013: 94.5**
**2014: 92.2**
**2015: 85.7**
**2016: 81.4**
**2017: 72.2**

- Abstract: should say in the Methods that the exposure was quintiles of ADI -- this is not mentioned until the Abstract conclusion

**Thank you for your comment. We have updated the text to reflect this change.**
- Strengths and Limitations: "This study is limited by potential imputation" -- more detail is needed by what is meant here. Do you mean that there could be bias due to non-trivial missing data?
**This study is limited by potential bias in the imputation given that some data may not be missing at random. Use of single imputation using regression assumes that the data are missing at random (MAR), but that these missing values can be estimated by a linear combination of the non-missing covariates. If the data is missing not at random (MNAR) – that is, missingness depends on the values of the missing data – then imputation will introduce bias to the results.**
**We added the following detail to the manuscript:**
**"However, our study had less than 1% missing data for each year and fewer than 80 variable observations were imputed in total. Thus, the potential for imputation bias is very low."**
- "All U.S. counties with opioid prescription and drug-poisoning mortality data available each year between 2012 and 2017 were included in the study sample. Counties without data for all six years of the study were excluded from the sample" (p. 7). Given that the analysis models annual county-level rates, couldn't counties that had at least one year of data be included?
**We included only those counties with prescribing and mortality data available each year of the study in order to most clearly examine the temporal changes in outcomes as a function of ADI and to present this data visually. Because only a small number of counties were excluded we do not believe this biased the results.**
- "County demographic information necessary for ADI derivation was ascertained from 2012-2016 and 2013-2017 5-year ACS estimates...calculated separately each year" (p. 7).
I found this language confusing -- how are the 5-year estimates calculated separately by year?
**The five-year estimates produce estimates for each individual year based on 60 months of data. We are pulling each respective years data based off 5-year pooled estimates which are arguably more accurate than 1-year estimates according to the ACS. We clarify this in the manuscript.**
- "We calculated modified ADI scores, using the Singh method,15 for all 3,142 counties in the U.S. using 5-year ACS estimates (Figure 3)." Is there a single ADI score per county, or could the scores vary over time?
**The scores can vary over time and were calculated separately for each year of the study. Weights for the variables for each year of the study are included in Table S1.**
- One suggestion to improve the paper flow would be to move the description of the exposure to its own section above the "Statistical Analysis" section. Then the Statistical Analysis section can focus on how you estimated the effect of the exposure (ADI quintile) on each of the outcomes
**Thank you for this suggestion. We have incorporated these changes.**
- "Predicted margins for adjusted prescription rates and drug-poisoning mortality were assessed by ADI quintile across all years." More details are needed on exactly what was done here, or at least a citation should be provided.
**We have included a citation for the predicted margins.**
- "county-level estimates for age" were adjusted for in the model. There are many options for this (e.g., mean or median age, % within different categoreis). What exactly was done?
**County level estimates were the % within different categories listed in the tables and under "statistical analysis". These estimates were ascertained from ACS.**
- How did the authors handle the ICD-9 to ICD-10 transition that occurred during the study period?
**We used publicly available data from the CDC, such that the ICD-9 to ICD-10 transition was addressed and accounted for by them.**
- In the results section is is difficult to tell whether estimates being presented are from fitting a model, or whether estimates are raw rates, when describing the trends in prescriptions (e.g., paragraphs 1-2 of Results).
**We regret the confusing language and revised the manuscript to be more clear. We specifically note that the estimates are adjusted, as contrasted to crude, and hence are derived by fitting a model.**
- Figure 2: Are these the raw rates or the smoothed rates from fitting the spatial-temporal model. These rates look a lot smoother than I would expect if they are the raw rates.
**As mentioned above, these are adjusted, not crude, rates.**
- Point estimates for Q5 are lower than for Q4 of the ADI in Figure S1, but in Table 1 Q5 has a higher IRR than Q4. Could you explain this seeming discrepancy?

**Thank you for bringing this to our attention. The figure presented was predicting values based on an average ADI across all years which we now appreciate to be confusing given the presentation of the other data. We have fixed this and revised the figure accordingly.**
- Models assume that the IRR of ADI quintile with the outcomes is constant by year; did you test this assumption?
**We tested the model by including an interaction term between ADI and year. Overall the interaction in almost all years and quintiles was not statistically significant (p value >0.05). In addition, our IRRs for ADI remained consistent with what we saw in the model that did not include the interaction of ADI*year.**
- "Each successively less deprived ADI quintile displayed a smaller decrease in prescription rate." (p. 10). Is this referring to descrease over time? Again, this sounds like you are commenting on interaction between ADI and calendar time (see related comment above), which was not explicitly modeled.
**Thank you for bringing this to our attention. We have updated the language in the manuscript.**
- "Although the absolute opioid prescription rate decrement was largest in ADI Q5, the proportion of the decrease was similar across all ADI quintiles." I found this sentence confusing. Perhaps the authors could point to the specific estimates and/or Figure that this is referencing. What do you mean by "decrement" -- does this mean change over time, or are you refering to an IRR < 1?
**We have updated the text to make this sentence less confusing and clarified that it is referring to the values from the predicted margins output.**
- Did the authors consider the potential for confounding by region. Some regions may have greater deprivation and also greater rates of opioid prescriptions and/or drug poisoning mortality, regardless of their deprivation. May want to present results stratified by region in a supplement.
**The goal of our paper was to show that deprivation, opioid prescribing, and drug-poisoning mortality are all interconnected. Our data does not allow us to tease out causality among the 3 by region. We have considered doing positive deviance analyses with this topic for a future paper and will consider incorporating confounding by region as well for that manuscript if we have the appropriate data.**
- "There were no major geospatial changes in the patterns of deprivation, opioid prescriptions, or drug-poisoning mortality during the study period" (p. 12). This is a strong assertion. How was this tested in the data?
**We did not test for temporal changes in geospatial patterns and revised our language so as to avoid this impression. We note that the patterns were visually and qualitatively comparable over time.**
- I'd suggest to include in the footnote to Figure 4 a 1-sentence description of the model including the covariates.
**We have addressed this comment.**

## VERSION 2 – REVIEW

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| **REVIEWER** | Bradley Stein<br>RAND Corporation<br>USA |
| **REVIEW RETURNED** | 03-Mar-2020 |

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| **GENERAL COMMENTS** | I appreciate the authors responses and revisions. I think they were able to address some of the issues raised by the reviewer, but many of the more fundamental issues that diminished my enthusiasm, and were echoed by other revieweres, remain. Let me highlight the most significant.<br><br>1) There is a substantial amount of research that has already examined the relationship between socioeconomic factors and opioid related outcomes. The authors are correct as far as I'm aware that no one has created a composite, but if the findings between the singular constructs and the composite are essentially the same, I'm unclear why the authors believe the composite is better. One might |

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| | even argue that the parsimony and simplicity of singular constructs that can easily be obtained is better than a composite that requires time and effort to construct.<br>2) It is well known that opioid analgesic prescribing rates have been falling while opioid related mortality has been increasing- the benefits of describing these well known trends in the same paper, beyond what is already known, is unclear to me. Furthermore, its pretty clear from a range of empirical studies that this phenomena is due to illicit opioids, primarily heroin from 2011-2015 and fentanyl and other synthetics since 2015, but this receives little attention from the authors.<br>3) The authors seem to argue that the deprivation index allows one to predict at-risk communities that will suffer opioid related harms so interventions could be deployed proactively. But there seems to be a number of issues with this argument, including a) the analysis they conducted examined associations and did not appear to examine the predictive value of the ADI and b) it is unclear that the ADI has any greater predictive value than a singular construct such as poverty rate that is commonly associated with a range of poorer health outcomes and easily obtained. If the authors believe a composite has greater predictive value, I would strongly encourage them to consider a paper comparing the predictive value of a composite to commonly used singular constructs. If the composite did have better predictive value, such a finding would have substantial value.<br><br>Unfortunately, I think the contributions of the current paper are far more modest given what we already know. |

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| **REVIEWER** | Jennifer Bobb<br>Kaiser Permanente Washington Health Research Institute |
| **REVIEW RETURNED** | 25-Feb-2020 |

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| **GENERAL COMMENTS** | Thank you for addressing my questions about the modeling approach.<br><br>- Imputation bias is listed as a limitation under "Strengths and Limitations of this Study" (p. 5). However, given that the authors report in their response that variables for 80 observations were imputed out of 320,484 observations (0.02%), any potential bias due to would be so small as to be trivial. Given the other limitations of this cross-sectional analysis, this tiny amount of missing data may not be warranted to be included as one of the main limitations.<br><br>- I appreciate the authors description of their exploration to how sensitive their modeling results were to their model assumptions in their response. They mentioned that their results did not change much, but I did not see where the limitations of their analysis approach were described in the discussion. Perhaps 1-2 sentences could be added to the discussion to explain how their SEs could be incorrect due to not accounting for uncertainty in the modeled outcome rates or to spatial autocorrelation. I was also a little confused by their exploration, as it considered a model that did not adjust for population size, whereas the manuscript text says that population size was accounted for.<br><br>- Minor: the text says that the negative binomial model controled for county population size, but it did not explicitly say that it was acounted for via an offset term. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 3

Reviewer Name
Jennifer Bobb

Institution and Country
Kaiser Permanente Washington Health Research Institute

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
Thank you for addressing my questions about the modeling approach.

- Imputation bias is listed as a limitation under "Strengths and Limitations of this Study" (p. 5). However, given that the authors report in their response that variables for 80 observations were imputed out of 320,484 observations (0.02%), any potential bias due to would be so small as to be trivial. Given the other limitations of this cross-sectional analysis, this tiny amount of missing data may not be warranted to be included as one of the main limitations.

**We agree with the reviewer and removed this from the limitations.**

- I appreciate the authors description of their exploration to how sensitive their modeling results were to their model assumptions in their response. They mentioned that their results did not change much, but I did not see where the limitations of their analysis approach were described in the discussion. Perhaps 1-2 sentences could be added to the discussion to explain how their SEs could be incorrect due to not accounting for uncertainty in the modeled outcome rates or to spatial autocorrelation. I was also a little confused by their exploration, as it considered a model that did not adjust for population size, whereas the manuscript text says that population size was accounted for.

**We apologize for the confusion. The analysis presented in the manuscript did account for county population size. We have included a sentence in the discussion about how the standard errors may be incorrect. “Lastly, the standard errors may be impacted by potential spatial autocorrelation and uncertainty in the modeled outcome rates.”**

- Minor: the text says that the negative binomial model controlled for county population size, but it did not explicitly say that it was accounted for via an offset term.

**We have specified that the population size was adjusted using an offset term. “We used negative binomial regression to examine the relationships between ADI and opioid prescription rates and drug-poisoning mortality from 2012 to 2017, controlling for over-dispersion of outcome estimates and county population size using an offset term.”**

Reviewer: 1

Reviewer Name
Bradley Stein

Institution and Country
RAND Corporation
USA

Please state any competing interests or state ‘None declared’:
none declared

Please leave your comments for the authors below
I appreciate the authors responses and revisions. I think they were able to address some of the issues raised by the reviewer, but many of the more fundamental issues that diminished my enthusiasm, and were echoed by other revieweres, remain. Let me highlight the most significant.

1) There is a substantial amount of research that has already examined the relationship between socioeconomic factors and opioid related outcomes. The authors are correct as far as I'm aware that no one has created a composite, but if the findings between the singular constructs and the composite are essentially the same, I'm unclear why the authors believe the composite is better. One might even argue that the parsimony and simplicity of singular constructs that can easily be obtained is better than a composite that requires time and effort to construct.

**We appreciate the reviewer's feedback on composite measures. Various papers have used composite measures such as the area deprivation index and there is evidence to suggest it is highly associated with health outcomes. Below are a few references:**
**- Knighton AJ, Savitz L, Belnap T, et al. Introduction of an area deprivation index measuring patient socioeconomic status in an integrated health system: implications for population health. eGEMs 2016;4(3)**
**- Liaw W, Krist AH, Tong ST, et al. Living in "cold spot" communities is associated with poor health and health quality. The Journal of the American Board of Family Medicine 2018;31(3):342-50.**
**- Kind AJ, Jencks S, Brock J, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. Annals of Internal Medicine 2014;161(11):765-74.**

2) It is well known that opioid analgesic prescribing rates have been falling while opioid related mortality has been increasing- the benefits of describing these well known trends in the same paper, beyond what is already known, is unclear to me. Furthermore, its pretty clear from a range of empirical studies that this phenomena is due to illicit opioids, primarily heroin from 2011-2015 and fentanyl and other synthetics since 2015, but this receives little attention from the authors.

**Thank you for this feedback and we agree that illicit opioids play an important role in drug poisoning mortality. We acknowledge this in the manuscript, but did not focus on illicit drugs in greater detail because this was not the focus of our study.**

3) The authors seem to argue that the deprivation index allows one to predict at-risk communities that will suffer opioid related harms so interventions could be deployed proactively. But there seems to be a number of issues with this argument, including a) the analysis they conducted examined associations and did not appear to examine the predictive value of the ADI and b) it is unclear that the ADI has any greater predictive value than a singular construct such as poverty rate that is commonly associated with a range of poorer health outcomes and easily obtained. If the authors believe a composite has greater predictive value, I would strongly encourage them to consider a paper comparing the predictive value of a composite to commonly used singular constructs. If the composite did have better predictive value, such a finding would have substantial value.

**Thank you for this suggestion and we will certainly consider this for a future study.**

Unfortunately, I think the contributions of the current paper are far more modest given what we already know.